the ζ chain initiates a signal. That is in contrast to the α and β chains which have a recognition function but do not initiate a signal, see page 3, lines 13-15 of the instant application.

I. In item 7 on page 3 of the Office Action, claims 64, 65, 67, 69 and 71 were rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-21 of U.S. Patent No. 5,359,046.

A Terminal Disclaimer will be filed shortly.

II. In item 8 on page 3 of the Office Action, claims 65 and 69 were rejected under 35 U.S.C. §112, first paragraph.

The Examiner stated that all cells inherently contain MHC antigens. Therefore the Examiner does not understand how a claim can recite that a cell is substantially free of surface expression of at least one of Class I or Class II MHC antigens.

The rejection is traversed for the following reasons.

It is known that not all cells express MHC antigens to the same extent and that some cells effectively do not express MHC antigens and thus, for example, are not viewed as foreign by a host.

Also, the specification teaches at page 22 manipulating the cells to prevent expression of one or both class I and II antigens so that those cells are "invisible" to the host. For example, it is known that proper expression of MHC requires the proper expression of β_2 microglobulin. Hence, blocking expression of β_2 microglobulin would result in the blockage of MHC expression, see the attached excerpt from, "The Role of the Major Histocompatibility Complex in Immunobiology", Dorf, ed. which teaches that it was known in 1981 that β_2 microglobulin expression is required for proper MHC expression.

Regarding the issue of stem cells, it was well known that stem cells can be found in bone marrow and techniques of bone marrow aspiration were well known. Thus, obtaining a population of cells from bone marrow for obtaining hematopoietic stem cells in culture was known. See page 24 of the instant specification which teaches hematopoietic stem cells as well as the attached copy of U.S. Pat. No. 4,965,204 which teaches isolating hematopoietic stem cells.

Hence, it is believed that the disclosure relating to the two issues raised by the Examiner regarding cells not expressing MHC and obtaining hematopoietic stem cells is enabled sufficiently in the teachings of the instant specification in view of the state of the art. Accordingly, withdrawal of the rejection is in order.

III. In item 9 on page 4 of the Office Action, claim 64 was rejected under 35 U.S.C. §112, second paragraph.

The Examiner stated that because there are two different uses of the word, "protein", in the claim, it is unclear as to the meaning of that word and therefore the claim itself.

The ambiguity has been addressed and overcome by the above amendment introducing, "chimeric", before the second occurrence of, "protein". Hence, the rejection can be removed.

IV. In item 10 on page 4 of the Office Action, claim 67 was rejected under 35 U.S.C. §112, second paragraph because the Examiner said it is unclear and thus indefinite as to what the term, "substantially free", means. Furthermore, the Examiner stated that it is ambiguous how T lymphocytes can be free of MHC antigens.

The rejection could be considered improper as the language at issue does not appear in claim 67.

Claim 69 does include such language. As discussed hereinabove, it is known that certain cells do not express effective amounts of MHC antigens. Also, it is known how to manipulate a cell so that MHC antigens are not effectively expressed at the cell surface. As noted at page 22, lines 10-16 of the instant specification, it is noted that the level of MHC

expression can be modified so that the cell is not recognized by the host system. That would be clear to the artisan on reading the claim and the instant specification.

Claim 69 depends on claim 64 and thus does not relate specifically to a cytotoxic T cell. Claim 67 which does relate to a cytotoxic T cell does not per se relate to expression of MHC. Therefore, the issue raised by the Examiner as to expression of MHC on T cells appears to be a non sequitur. However, as discussed in the instant specification, a cytotoxic T cell, for example, could be manipulated to not express β_2 microglobulin and thus that T cell would not express MHC antigens.

Accordingly, it is believed claims 67 and 69 and clear, distinct and describe the invention of interest in terms which are readily interpretable by an artisan. Hence, withdrawal of the rejection is in order.

V. In item 11 at the bottom of page 4 of the Office Action, claims 57, 64, 67, 69 and 71 were rejected under 35 U.S.C. §102(b) over Gross et al.

Also, in item 12 on page 5 of the Office Action, claims 57, 64, 67, 69 and 71 were rejected under 35 U.S.C. §102(b) over Kuwana et al.

The two anticipation rejections are traversed for the

following reasons.

Gross et al. teach the T body approach wherein the intracellular domain of a chimeric receptor is obtained from either the α or ß chain of the T cell receptor.

The instant claims recite that the cytoplasmic domain is one which initiates a signal.

The instant inventions is distinguishable because the cytoplasmic domains of α and ß chains do not initiate a signal and it is highly questionable whether one could say that the α and β chains transduce a signal. While the α and β chains are involved in the signalling process, autonomously, those chains cannot and do not signal. See, for example, Tan et al., J. Exp. Med., 173, 1247-1256, 1991, copy attached hereto. The Summary thereof teaches that the α and ß chains recognize antigen whereas CD3 chains transduce signal. See, also Weiss, J. Clin. Invest., 86, 1015-1022, 1990, which teaches at page 1016, left column, that the T cell receptor is comprised of an antigen binding subunit and a signal transduction subunit. See Figure 1 which demonstrates the minimal cytoplasmic domain of the α and ß chains. It is known that the α and β chains are responsible for the antigen binding activity of the T cell receptor. Therefore, it is clear that at the time of the invention, α and β were known not to initiate a signal.

Page 18 of the instant specification teaches a T cell receptor deficient Jurkat cell line which when transformed with a receptor of interest nevertheless was able to support signalling in the

presence of a chimeric receptor of interest. Therefore, the instant receptors, which contain, for example, ζ as the intracellular domain, signal independent of the intact T cell receptor.

On the other hand, in Gross et al., the α/ß-containing receptor constructs were introduced into a cell which contained intact T cell receptor. See page 10026, lines 5-6 of Gross et al., which teach that MD45 lyses target cells. Therefore, the α/ß chimeras of Gross et al. interact with intact T cell receptor to obtain antigen-specific signalling because as was known in the art at the time of Gross et al., α and ß chains do not signal autonomously.

Therefore, Gross et al. do not teach an autonomously signalling chimera. Hence, anticipation does not exist and the rejection can be removed.

The Kuwana et al. receptors, as do the Gross et al. receptors, comprise α and ß chains as the intracellular domains thereof. Thus, all of the arguments for distinguishing over Gross et al. provided hereinabove are applicable to distinguish the instant invention over Kuwana et al. Accordingly, those arguments distinguishing over Gross et al. are incorporated by reference herein as applied to Kuwana et al. as well.

The Kuwana et al. receptors do not signal autonomously and do not initiate a signal.

Hence, Kuwana et al. do not anticipate the instant invention.

Therefore, the rejection can be removed.

CONCLUSION

It is believed the application now is in condition for allowance. Reconsideration, withdrawal of the rejections and early indication of allowance are solicited earnestly.

Applicants hereby petition for any extension of time which may be required to maintain the pendency of the instant application and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,

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